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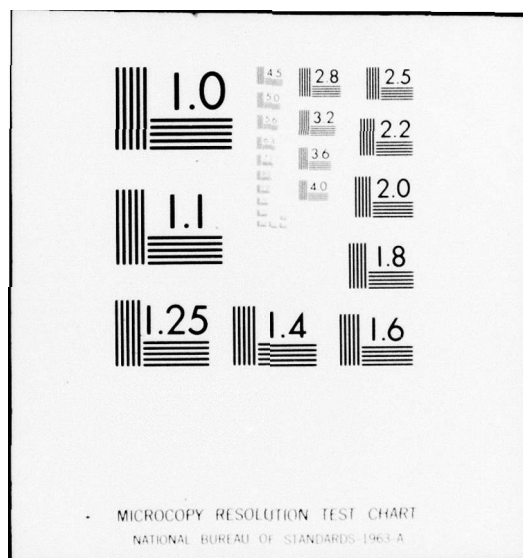
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Morphological studies of experimental epidemic encephalitis (summer-encephalitis). (II. report) Regarding modifications of intracranially, nasally, intravenously and subcutaneously injected mice, with special consideration of the relation between the infection-mode and its distribution. Fumikazu Takaki, Institute of Pathology of the Imperial

University of Tokyo. Head of Department: Prof. T. Ogata and Prof. T. Mitamura.

The following study<sup>was</sup> intended to examine the expansion-mode and the development of encephalitic changes of epidemic encephalitis (the Japanese summer-encephalitis) of mice; caused by experimenting on various modes of injection, such as intracerebralic, intranasal, intravenous and subcutaneous injections. At the same time reactions of the intestines, especially of the fibrous tissue of the vascular system were considered. Since this report does not put me into the position to give detailed description of the individual findings, I will only provided a short summary of the experimental results.

#### Method of procedure:

19 to 20 of ordinary young mice at a time (weight: 6-11 g) injected with a 10 % emulsion of infected mice-brains (Calina lineage): intracerebral (0,03 ccm), intranasal (0,4 ccm), intravenous (0,1 ccm or 2 % emulsion 0,2 ccm) and subcutaneous (0,4 ccm). An autopsy was performed in various intervals of time after the injections, that is 1,2,3,4,5,6,7,8,9,10, 11, 12, 13, 14, 15, 16, 17 etc days. Animals of the intracranially injected group became ill, or all the remaining ones died within 5 days. Of the intranasally in-

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ected group within 6 - 10 days. Whereas of the intravenously injected group only 7 of 12 remaining animals showed positive results. Of those injected subcutaneously no symptoms were observed. Brains and spinal cord were fixed in formalin, decalcified and embedded in paraffin. Frontally resp. laterally successive sections (intervals 30 - 40 micron) were tinted with haematoxylin-eosin. H.e.tinted preparations of the lungs, liver, spleen, lymphnodes and heart were examined.

Development of encephalitic modifications:

The development is substantially the same in all four groups. Also individual findings emphasize reports of authors (Mitamura, Kawamura etc.). Only after a certain period of incubation (intracranially injected group 1-2 days), intranasally infected group (4-5 days), intravenously injected group (4-6 days ) hyperemia of the soft meninges and the cerebral matter, cellular infiltration of the soft meninges and vessels (vascular wall and the perivascular area), and an occasional capillary bleeding (diapedetic bleeding) would occur. Gradually modifications of this kind will become very noticable and in addition there will be a reaction of the adjoining cerebral matter (infiltrations of tissue): a rather diffused, inflammatory cellular infiltration and mobilization of the horticaglia. The latter may occasionally occur independant of vascular infiltration. Simultaneously regressive modifications of the ganglion cells can be observed. Finally the inflammatory reaction will become very noticable and diffused. There are rather strong regressive modifications of ganglion cells (serious and lighter degeneration, necrosis, atrophy etc.) at this stage, but in comparison to inflammatory modifications they are not as strong. There is softening of cerebral matter, degenerative modifications of a mobilized horticaglia etc. in areas of severe inflammation. At this point

the animal usually dies. Of especially lymphocytic nature are the cells to be infiltrated, occurring in rather large numbers. There are apparently more of them in heavily infiltrated areas. In addition to these, histiocytic cells and plasmacells are found in various numbers but not as many of the lympho- and leucocytic ones. Mobilization of adventitia cells and swelling of vascular endothelia is generally to be observed. The vascular infiltrates are primarily found in venes. Regressive modifications of ganglia cells are found mostly in severely inflamed areas of tissue, sometimes in spots unrelated to the latter. It is remarkable how relatively fast the ganglia cells of the Ammon's horn are affected. Furthermore there are no circumscribed glial nodes, neuronophagic and no circumscribed spotted necrosis of cerebral tissue, which is usually found with human encephalitis. With some of the animals of the intravenously and subcutaneously injected group which did survive the infections and had to be killed, 13 and 17 days after the injection, I was able to testify results of the late stage (subchronic resp. chronic stage). At this stage the reactions of glial elements is dominating: a proliferation of a diffused nodose and lawn-like nature of horticaglia and obligodendrogalia, with or without a very light swelling and mobilization of the macrogalia. There are also occasional findings of neuronophagy. Hyperemia and diapedetic bleedings along with inflammatory cellular infiltrations of the vessels and of the soft meninges are less obvious; and by this the modifications become more localized to areas which had already been damaged noticeably. As the relation between meningitis and encephalitic modifications I may say that meningeal cell-infiltration and perivascular infiltration of cerebral tissue happens at the same time, although modifications become more noticeable in the process. At this point the grey matter is affected more noticeably than the white one. When the

cerebral matter is heavily affected, adjoining ganglia, such as Gasserian ganglion and spinal ganglia, show an occasional light infiltration of round cells.

Mode of propagation:

A) Intracerebrally injected group:

There is discrimination between the control- and experimental animal, during the period of incubation as to the modifications around the region of intracerebral injection: extending from the parietal region deep down to the Ammon's horn and the thalamus region.

Now perivascular and meningeal cell-infiltration occur and also hyperemia in the vicinity of the puncture area. Gradually they spread out orally and caudally along the vessels and along the soft meninges. Necrosis, bleeding, inflammatory puncture area and mobilization of microglia become stronger too whereas with the control animal there is a gradually dominating reaction of the micro- and macroglia, promoting localization of bleeding and necrosis. Thus the most noticable modifications in the parietal region, thalamus and mid-brain, can be observed with the severely diseased animals or with those dying with typical symptoms. Other areas of the end-brain, marrow-brain, especially of the pons and medulla oblongata are most often affected by medium encephalitic modifications. Whereas very light modifications show in the spinal cord: more often and more noticably so in the upper part than in the lower part of it. The lower part quite often is not affected at all.

B) Intranasally injected group:

The olfactory mucous membrane soon after injection produces inflammatory modifications- very light at first- consisting of the loosened homogenous top layer and the hyperemia. While growing gradually stronger sporadic necrosis



of the olfactory cells can be noticed more often. During the period of incubation I could scarcely see any modifications on the fila olfactoria. Yet at a more advanced stage occasionally there is a very light infiltration of round cells around the vessels and nerve bundles. After a certain period of incubation hyperemia and cell infiltration of the soft meninges of the bulbusolfactorius occur. It travels downwards quite fast along the soft meninges and vessels to the base of the brain, i.e. lobus pyriformus, base of the brain, fissura hippocampi etc., as well as to the respective low parts such as nucleus caudatus, lentiformis, cornu Ammonis, thalamus, midbrain etc., all the way to the pons, little brain, medulla oblongata and the spinal cord. On the other hand it spreads out upward along the front and laterally along the mantle part of the end-brain.

Therefore the most noticable modifications are found in the area of bulbus olfactorius, lobus pyriformis, substantia perforata anterior et posterior, nucleus caudatus et lentiformis, thalamus and midbrain with animals seriously infected or with those dying in the process. There is usually a medium impact on the mantle part of the brain and marrobrain. The spinal cord reacts almost in the same manner as with the intranasally infected group.

C) Intravenously infected group:

This group produces a diffused distribution of modifications as opposed to the first and second group. This leads us to the conclusion that in this group encephalitic modifications are diffused immediately, affeting several parts of the central nervous system simultaneously.

But there are some preferred areas, i.e. 1) nucleus caudatus et lentiformis, 2) thalamus and midbrain region, 3) pons, medulla oblongata, 4) the spinal cord. At any rate these preferred areas are affected more noticably - though not to the same degree - than other parts of the central nervous system. Occasionally two of them are affected in the same degree and most noticably

so. Table I demonstrates how frequently the cases involved are damaged most noticeably in one or two regions of preference.

Table I

	N. caudatus N. lentiformis	Thalamus Mittelhirn	Pons Medulla ob.	Halsmark	Rückenmark Lendenmark Unterster Teil d. Brustmarks	Gesamte Fälle
Intracerebrale Verimpfung Gruppe 8	5	4	2	1	1	11
Subcutane Verimpfung Gruppe 7	1	0	0	1	2	1

- 1 = midbrain  
2 = cervical part of the medulla  
3 = spinal cord  
4 = lumbar part of the cord  
5 = thoracic cord  
6 = total number of cases  
7 = subcutaneously injected group  
8 = intravenously injected group

Where two regions were affected to the same degree they are listed for both of them

D) Subcutaneously infected group:

In this group I was able to single out only 4 animals which showed light or medium modifications of an acute or subchronic nature. The regions affected agreed in principal with those of the intravenously injected group. (Table I)

The findings of all animals obviously indicate a certain relationship between meningeal infiltration and the intensiveness of encephalitic modifications. e.g. between meningitis of the convexity and the affect upon the grey matter, between meningitis of the lobus pyriformis and the encephalitic modifications of the nucleus caudatus et lentiformis, between the basilar meningitis and the affect upon the inter- and midbrain. etc.

Reactions upon the viscera especially upon the connective tissue-system of blood vessels is basically the same with all four groups, although there are small distinctions as to the intensity of reaction. They are mainly bleedings

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of the lungs, inflammatory reactions of the mesendymal tissue of the liver, spleen and of the lymph-nodes. Also I was able to detect a light infiltration of cells in the peribronchal tissue and of the alveolarsepta

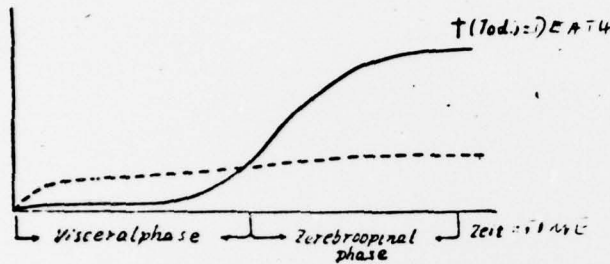


Fig. 1. Reactions of the central nervous system and the viscera in the process of time.

of the lungs. With some animals there is a very light infiltration of round cells into the myocardia. In comparing modifications of the central nervous system with these of the viscera, one will find that the latter are of a lighter degree than the first ones, while appearing earlier at the same time. (Fig. 1)

So I would like to suggest calling the earlier stage "visceral phase" in which reactions of the viscera, especially those of the connective tissue-system of blood vessels, are more dominant, and to call the later stage "cerebrospinal phase", which is characterized by the encephalitic changes.

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